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Reproducibility of Individual Responses to Ozone Exposure

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16. ABSTRACT

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Reproducibility of Individual Responses to Ozone Exposure[1-3]

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SUMMARY Because large intersubject differences in the magnitudes of response to a single ozone (O_3) exposure have been observed, we undertook to determine if this variability were due to differences in intrinsic responsiveness to O_3 or to other factors. Thirty-two subjects were exposed to 1 of 5 O_3 concentrations (0.12, 0.18, 0.24, 0.30, or 0.40 ppm), and each underwent one or more repeat exposures separated by from 3 wk to 14 months. Magnitudes of change for pulmonary function variables, respiratory rate and tidal volume, and for reported symptoms were compared for the repeated exposures. Changes induced in forced expiratory spirometric measurements were highly reproducible for as long as 10 months and for all tested O_3 concentrations of 0.18 ppm or greater. This high degree of reproducibility indicates that the magnitude of response to a single exposure is a precise estimate of that subject's intrinsic O_3 responsiveness. We conclude that the previously observed intersubject variability in magnitude of O_3-induced effects is the result of large differences in intrinsic responsiveness to O_3.

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Introduction

Acute changes in respiratory function and the induction of symptoms have been well documented after exposure to ozone (O_3) at levels commonly found in ambient air (1-3). Recent reports have indicated that otherwise similar persons differ markedly in the magnitudes of their responses to O_3 (3-5). Horvath and coworkers (5) have reported decrements in forced expiratory volume in one second (FEV_1) ranging from 2 to 48% in 24 subjects exposed to 0.42 ppm O_3 for 2 h while performing intermittent moderate exercise. McDonnell and associates (3) observed decrements in FEV_1 from 3 to 48% and changes in specific airway resistance (SRaw) from −20 to 80% in 29 healthy, nonsmoking young males exposed to 0.40 ppm O_3 for 2 h while performing intermittent heavy exercise. Differences of a similar range were reported in that study for subjects exposed to 0.30 and 0.24 ppm O_3, and smaller differences were reported at lower concentrations.

The question of whether some persons are reproducibly much more responsive to O_3 exposure than are others has not previously been adequately evaluated. Other possible explanations for the observed intersubject variability include lack of precision in measuring response, inability to produce identical exposure conditions for different subjects, or differences in airway responsiveness to O_3 caused by unidentified factors. Gliner and coworkers (4) have reported data demonstrating that individual changes in FEV_1 are reproducible when subjects are exposed twice to either 0.42 or 0.50 ppm O_3 for 2 h. This suggests that the large intersubject differences measured by changes in FEV_1 during high level O_3 exposures are primarily due to differences in the intrinsic responsiveness of individual subjects to O_3. Neither the degree to which these results are valid at lower O_3 concentrations or for variable time periods nor the degree to which other responses are reproducible have been determined.

The purpose of this study was to measure the reproducibility of individual changes in pulmonary function, respiratory rate and tidal volume, and symptoms for subjects undergoing similar O_3 exposures separated by different intervals of time and for pairs of exposures at different O_3 concentrations.

The results indicate that changes in spirometric measurements are highly reproducible at all levels of O_3 exposure greater than or equal to 0.18 ppm for a period of 3 months. Reproducibility decreased somewhat at 0.12 ppm O_3 and for exposures separated by longer intervals. Subjects' evaluations of the presence of cough were somewhat less reproducible, but the trend was similar. Other variables were generally less reproducible.

Methods

Healthy male volunteers, 18 to 30 yr of age, served as subjects for this study. They were recruited from a group of 115 former subjects who had participated in a previous study, and who had each been exposed once to either 0.12, 0.18, 0.24, 0.30, or 0.40 ppm O_3. Potential subjects were excluded from participation if they had smoked within 3 yr or had a history of asthma, allergic rhinitis, cardiac disease, chronic respiratory disease, recent acute respiratory illness, or extensive exposure to pollutants. All potential subjects underwent a physical examination and routine chemical and hematologic screens. Accepted subjects were informed of the purposes, experimental protocol, and procedures of the experiments, as well as potential risk from participation, and each signed a statement of informed consent. This study was approved by the Committee on the Protection of the Rights of Human Subjects of the University of North Carolina School of Medicine.

At least one day prior to exposure, subjects were trained in the techniques for obtaining plethysmographic and spirometric measurements. At this time they also exercised on a treadmill, and the speed and grade of incline required to produce a minute ventilation ($\dot{V}_E$) of approximately 35 L × min^{-1} × m^2 body surface area were determined. A few subjects were excluded at this point because of excessive heart rates associated with this level of exercise.

On the morning of exposure, subjects initially completed the symptom questionnaire and performed preexposure spirometry and plethysmography in clean air. They were then exposed to the appropriate O_3 concentration for 2.5 h. During the first 2 h of exposure, 4 cycles of 15 min of rest followed by 15 min of exercise were completed. Treadmill exercise was performed at the predetermined speed

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[2] Although the research described in this article was funded wholly by the United States Environmental Protection Agency, it has not been subjected to the Agency's required peer and policy review, and, therefore, does not necessarily reflect the view of the Agency, and no official endorsement should be inferred.

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and grade of incline. Measurements of $\dot{V}_E$, tidal volume (V_T), and respiratory rate (f) were obtained during the eleventh and twelfth minutes of each exercise period. Changes in exercise load were made for subjects whose $\dot{V}_E$ was markedly different from the 35 L × min^{-1} × m^2 seen during training or who developed excessively high heart rates. Spirometric and plethysmographic measurements were made 5 and 25 min, respectively, after the final exercise; 10 min after the final exercise, subjects again completed the symptom questionnaire.

Of the 32 subjects recruited from the previous study, 23 returned for 2 additional exposures for a total of 3 exposures (D_{31}, D_{32}, D_{33}), and 9 subjects were reexposed once for a total of 2 exposures (D_{21}, D_{22}). All exposures for each subject were conducted under identical conditions, and all possible pairs of exposures (D_{31}, D_{32} or D_{32}, D_{33}, or D_{31}, D_{33}) for each subject from the 3 exposure group were equivalent, except for the interval between exposure. The magnitudes of the individual responses for the 2 most recent exposures (D_{32}, D_{33} for the 3-exposure group, and D_{21}, D_{22} for the 2-exposure group) were compared in the main analysis for all 32 subjects as a group and by O_3 concentration. To measure the reproducibility over time, similar comparisons were made for the 27 subjects who had a pair of exposures separated by less than 150 days and for the 26 subjects who had a pair of exposures separated by more than 150 days. For the 2-exposure group, the interval for the pair of exposures (D_{21}, D_{22}) for each subject was determined and the pair was assigned to the appropriate analysis group. For the 3-exposure group, the pair with the longest interval (D_{31}, D_{33}) was determined, and if the interval exceeded 150 days, this pair was assigned to that group. The pair with the shortest interval was then determined (generally D_{32}, D_{33}), and if this interval was less than 150 days, this pair was assigned to that group. Each interval group had no more than one pair of exposures from each subject.

Spirometric measurements consisted of 3 forced vital capacity (FVC) maneuvers performed on a 12-L dry-seal spirometer (Model 220; Cardio-Pulmonary Instruments, Houston, TX). Graphic displays of each FVC maneuver were evaluated, and those interrupted by cough were discarded. The FEV_1 and mean expiratory flow rate between 25 and 75% FVC (FEF_{25-75}) were also calculated for each FVC maneuver. For each properly performed maneuver, FVC and FEV_1 were added, and the FVC, FEV_1, and FEF_{25-75} from the maneuver with the highest sum were used.

Airways resistance, thoracic gas volume, and SRaw were determined according to the method of DuBois. Briefly, subjects were seated in a standard, variable-pressure body plethysmograph (CPI model 2000TB) and panted at 1.5 Hz. Slopes of flow versus box pressure were measured between −0.5 and +0.5 L/s flow, and 2 to 6 breaths were averaged for calculation of each variable. Measurements were made in triplicate, although in some instances less than 3 satisfactory measurements were obtained; means of the measurements from all satisfactory maneuvers were used.

During exercise, measurements of $\dot{V}_E$, V_T, and f were obtained by digital integration of flow signals from a Fleisch no. 3 pneumotachometer; V_T and $\dot{V}_E$ were corrected to BTPS. Measurements of $\dot{V}_E$, f, and V_T were acquired during the eleventh and twelfth minutes of exercise, and running averages were calculated every 10 s. The means of these running averages at 12 min were used for analysis.

The symptom questionnaires contained 3 questions regarding the presence and severity of cough, shortness of breath, and pain upon deep inspiration. Subjects were asked to classify their responses to each question as none, mild, moderate, or severe. For purposes of statistical analysis, a score of 1 was assigned to none, 2 to mild, 3 to moderate, and 4 to severe.

For pulmonary function variables and symptoms, differences between preexposure and final measurements were calculated for each subject. For V_T and f during exercise, differences between measurements obtained during the first and fourth exercise periods were calculated. Data from subjects whose exercise intensity was changed during exposure were excluded from analysis of these variables. Measurements of $\dot{V}_E$ were averaged over all 4 exercise periods for each exposure for each subject.

Measures of reproducibility for pairs of exposures were calculated in 2 ways. The slope, intercept, and correlation coefficient (r) of the best fit linear regression line were calculated for the responses of Exposure 1 versus Exposure 2. These were tested for difference from 1, 0, and 0, respectively, by the *t* test. Slopes and intercepts for symptom scores were not reported. Because the symptom responses are not strictly continuous variables, we also calculated a Spearman's rank correlation coefficient for symptom variables. The correlation coefficient does not strictly test for reproducibility of response if the best fit regression line deviates from the line of identity. For this reason, an intraclass correlation coefficient (R) was also calculated as the proportion of the total (intersubject plus intrasubject) variance accounted for by the intersubject variance (6). This essentially measures how closely the data from repeat exposures fit the line of identity, and it is a direct measure of reproducibility. The R was tested for difference from zero by a variance ratio from an analysis of variance technique (6).

Further evaluation for systematic differences in mean O_3 response, experimental conditions, or baseline measurement between the first and second exposure of an analysis was accomplished by performing a paired *t* test.

Because of the number of statistical tests performed, no p value greater than 0.01 was considered significant.

Exposures and measurements were conducted in a stainless steel chamber 4 by 6 by 3.2 m maintained at 22° C and 40% relative humidity. Ozone was generated by passing incoming "makeup" air over ultraviolet lights. The concentration of O_3 in the chamber was continuously monitored by chemiluminescence detection using Bendix Model 8002 analyzers (Ronceuerte, WV), which were periodically calibrated against an ultraviolet ozone photometer (Dasibi Model 1003AH, Glendale, CA). A detailed description of the chamber and the O_3 generating, delivery, monitoring, and control systems has been previously published (7, 8).

Results

Thirty-two subjects were exposed at least twice to 1 of 5 O_3 concentrations. The 2 most recent exposures for each subject were separated by an average of 88 days (range, 21 to 385). Preexposure measurements of spirometric variables and SRaw were not significantly different for the 2 exposures (table 1). Measurements of $\dot{V}_E$ during exposure were not significantly different for the 2 exposures, and average O_3 concentration never varied by more than 0.004 ppm for any pair of exposures.

Correlation coefficients comparing, for these 2 exposures, individual changes in FVC, FEV_1, and FEF_{25-75} ranged from 0.83 to 0.92 (figure 1 and table 2). All were statistically different from 0. The slopes and intercepts of these regression lines were quite close to 1 and 0, respectively, for FVC and FEV_1, and slightly

TABLE 1

BASELINE CHARACTERISTICS AND EXPOSURE CONDITIONS FOR REPEAT EXPOSURES*

	$\bar{X}_1$†	$\bar{X}_2$†	r	a	b
FVC, L	5.44 ± 0.74	5.44 ± 0.74	0.97	0.22	0.96
FEV_1, L	4.47 ± 0.57	4.48 ± 0.60	0.97	−0.02	1.01
SRaw, cm·s	3.99 ± 1.34	3.84 ± 1.10	0.85	1.05	0.71
$\dot{V}_E$, L/min	65.9 ± 8.4	66.4 ± 9.3	0.77	1.01	0.85

Definition of abbreviations: $\bar{X}_1$ = mean for exposure 1; $\bar{X}_2$ = mean for exposure 2; r = correlation coefficient; a = intercept of regression line; b = slope of regression line; FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second; SRaw = specific airway resistance; $\dot{V}_E$ = minute ventilation.

* Number of subjects = 32.

† Values are mean ± SD.

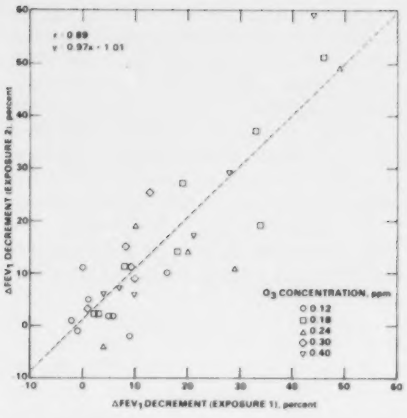

Fig. 1. Comparison of the percent decrement from baseline in forced expiratory volume in one second (FEV_1) for subjects exposed to ozone on 2 separate occasions. Each subject was exposed twice under similar conditions to 1 of 5 ozone concentrations. The dashed line is the least squares regression line.

less so for FEF_{25-75} and SRaw. None were statistically different from 1 and 0, respectively. Correlation coefficients for changes in cough, SRaw, and shortness of breath were lower than for spirometric variables, but were still statistically different from 0. Correlation coefficients for pain on deep inspiration, VT, and f were much lower and not statistically different from 0. The regression lines for changes in VT and f deviated markedly from the line of identity. Spearman's correlation coefficients and their associated p values for symptoms were almost identical to the reported values derived from linear regression.

Values of the intraclass correlation coefficient (R) were similarly highest for changes in FVC and FEV_1 followed by changes in FEF_{25-75} and then by cough. For changes in SRaw and shortness of breath, R was considerably smaller, though still significantly greater than 0. Changes in pain upon deep inspiration, VT, and f were not reproducible, as evidenced by the R not being significantly greater than 0, and no further analyses were performed on these variables.

Examination of data at individual O_3 concentrations (table 3) revealed that, in general, the R at each level greater than or equal to 0.18 ppm was approximately equal to the R for all levels considered together (tables 2 and 3). The R was generally lower in the 0.12 ppm O_3 group than in the other groups, and was in no case significantly greater than 0.

With longer intervals between exposures, the R for changes measured by spirometry or during cough were somewhat smaller (table 4). For SRaw and shortness of breath, the R increased somewhat with increasing intervals. All intraclass correlation coefficients were significantly greater than 0 at both intervals.

Discussion

The purpose of this study was to measure the reproducibility of responses to O_3 exposure so that conclusions could be drawn about the significance of the observed wide ranges in individual responses to a single O_3 exposure (3–5). In particular, we wanted to know if this intersubject variability is primarily due to real differences in O_3 responsiveness among subjects or whether it can be accounted for by such factors as the lack of precision inherent in making pulmonary function measurements, inability to provide identical exposure conditions, or other sources of variability.

For all variables except f and possibly VT, it is unlikely that differences in exposure conditions or baseline lung function account for a large proportion of the intersubject variability observed in this study and in previous studies. The O_3 concentration, an established determinant of magnitude of response, was very reproducible for repeat exposures in this study. Although $\dot{V}E$, another determinant of magnitude of response, was less reproducible from one exposure to the next, the range of ventilation among subjects and exposures was small relative to the mean value. Furthermore, Folinsbee and coworkers (2) have demonstrated that measures for all variables except f are much less sensitive to changes in $\dot{V}E$ than to changes in O_3 concentration. The use of differences between preexposure and postexposure measurements as the response variables adjusts for small differences in preexposure measurements.

Although the standard r measures the goodness of fit of points to a regression line, it does not give any information about lack of reproducibility caused by deviations of the best fit regression line from the line of identity. Assessment of reproducibility using linear regression requires simultaneous evaluation of the r, slope, and intercept. The intraclass correlation coefficient (R), on the other hand, directly measures reproducibility of responses and combines all the information contained in the r, slope, and intercept into a single measure, R. This, in effect, is a measure of how closely data fit the line of identity.

For the changes in FVC and FEV_1 measured during 2 exposures in this study, the large R (table 2) indicates that these responses are very reproducible relative to the total variability among subjects. This implies that either the subjects had large differences in intrinsic responsiveness to O_3 or that the large range of response was due to the use of 5 different concentrations of O_3. Because there was little difference in the ranges and the means of responses for the 4 higher O_3 concentrations (figure 1), and because the R for each of the O_3 concentrations greater than or equal to 0.18 ppm O_3 (table 3) was generally similar to the overall R (table 2), we conclude that for O_3 exposures greater than or equal to 0.18 ppm,

TABLE 2

CHANGES INDUCED IN RESPIRATORY FUNCTION AND SYMPTOMS BY REPEAT OZONE EXPOSURES*

	$\overline{\Delta X}_1$†	$\overline{\Delta X}_2$†	r	a	b	R
FVC, L	−0.56 ± 0.64	−0.56 ± 0.70	0.92‡	0.01	1.01	0.92‡
FEV_1, L	−0.64 ± 0.70	−0.66 ± 0.75	0.91‡	−0.04	0.97	0.91‡
FEF_{25-75}, L/s	−0.96 ± 1.03	−1.02 ± 1.07	0.83‡	−0.19	0.86	0.83‡
SRaw, cm·s	0.48 ± 0.70	0.65 ± 1.04	0.58‡	0.24	0.86	0.54‡
Cough§‖	0.9 ± 0.8	0.9 ± 0.7	0.76‡	—	—	0.77‡
SB§‖	1.1 ± 0.7	1.0 ± 0.8	0.61‡	—	—	0.60‡
PDI§¶	1.0 ± 0.7	1.0 ± 0.9	0.37	—	—	0.37
VT, L**	−0.43 ± 0.25	−0.29 ± 0.22	0.02	−0.28	0.02‡	−0.03
f, 1/min**	7.0 ± 5.3	5.9 ± 5.8	−0.22	7.54††	−0.24‡	−0.20

Definition of abbreviations: $\overline{\Delta X}_1$ = mean change from baseline for exposure 1; $\overline{\Delta X}_2$ = mean change from baseline for exposure 2; R = intraclass correlation coefficient; FEF_{25-75} = mean expiratory flow rate between 25 and 75% of FVC; SB = shortness of breath; PDI = pain upon taking a deep inspiration; VT = tidal volume; f = respiratory rate. For other abbreviations, *see* table 1.

* Number of subjects = 32.

† Values are mean ± SD.

‡ $p < 0.001$ for r, a, R = 0, and b = 1.

§ Presence and severity of symptoms are scored as 1 for none, 2 for mild, 3 for moderate, 4 for severe. Slopes and intercepts not calculated for discreet variables.

‖ Number of subjects = 31.

¶ Number of subjects = 29.

** Number of subjects = 18.

†† $p < 0.01$ for r, a, R = 0, and b = 1.

TABLE 3

INTRACLASS CORRELATION COEFFICIENTS FOR CHANGES INDUCED BY REPEAT EXPOSURE FOR FIVE CONCENTRATIONS OF OZONE (ppm)

	R				
	0.12 O_3 (n = 8)	0.18 O_3 (n = 8)	0.24 O_3 (n = 5)	0.30 O_3 (n = 5)	0.40 O_3 (n = 6)
FVC, L	0.26	0.97*	0.88†	0.88†	0.87†
FEV_1, L	0.57	0.94*	0.88*	0.56	0.91*
FEF_{25-75}, L/s	0.45	0.90*	0.83	0.35	0.85†
SRaw, cm·s	0.38	0.62	0.96*	−0.72	0.48
Cough	0.64‡	0.78†	0.80	0.70	1.00*
SB	0.05‡	0.46	0.71	0.58	0.88†

For definition of abbreviations, see tables 1 and 2.
* $p < 0.001$ for R = 0.
† $p < 0.01$ for R = 0.
‡ Number of subjects = 7.

the intersubject differences in magnitude of change in FVC and FEV_1 are due primarily to differences in intrinsic responsiveness to O_3 exposure.

The values for the slope, intercept, and r for percent changes in FEV_1 (figure 1) in this study are comparable to those reported by Gliner and coworkers (4) who exposed healthy nonsmoking men and women to either 0.42 or 0.50 ppm O_3 while they underwent a 2-h exposure to O_3. The interval between exposures was not specified. They reported an r of 0.92, a slope of 1.13, and an intercept of 1.06.

The data in table 4 suggest that the reproducibility for FVC and FEV_1 diminishes somewhat with time. Some loss of reproducibility may occur over time because of the difficulty in insuring that subjects perform maneuvers in exactly the same manner as during prior exposures. Subjects were not studied for 6 wk after an upper respiratory infection or for 3 wk after a prior O_3 exposure because these are factors that have been shown to alter airway responsiveness to methacholine (9) and O_3 (5, 10), respectively. It is possible that other intercurrent environmental or other undescribed factors may produce changes in a subject's responsiveness to O_3. Because the data in table 4 are neither fully paired nor independent, statistical evaluation of the differences over time is inappropriate, and we cannot rule out chance as the explanation. In any case, a significant amount of intersubject variability is still accounted for by differences in intrinsic responsiveness to O_3, and we conclude that these differences are maintained over periods of time as long as 10 months.

TABLE 4

INTRACLASS CORRELATION COEFFICIENTS FOR CHANGES INDUCED BY REPEAT OZONE EXPOSURES SEPARATED BY DIFFERENT INTERVALS

	R	
	Pair 1 (48 ± 30 days)* (n = 27)	Pair 2 (301 ± 77 days)* (n = 26)
FVC	0.94†	0.76†
FEV_1	0.94†	0.79†
FEF_{25-75}	0.85†	0.75†
SRaw	0.53†	0.70†
Cough	0.79†	0.71†
SB	0.53‡	0.71†

Definition of abbreviations: Pair 1 = pairs of exposures separated by less than 150 days; Pair 2 = pairs of exposures separated by more than 150 days. For definition of other abbreviations, see tables 1 and 2.
* Values are mean ± SD for length of time between repeat exposures.
† $p < 0.001$ for R = 0.
‡ $p < 0.01$ for R = 0.

The implications of large intersubject differences in intrinsic responsiveness to O_3 as measured by FVC and FEV_1 are twofold. For acute ambient exposures to O_3, some subjects will consistently have larger acute changes in spirometric variables than will others. This may result in a diminished ability to perform physically or in increased discomfort for the most responsive. The implications for recurrent ambient exposure are less clear, but of potentially greater importance. Although the mechanisms of changes in spirometric variables after O_3 exposure have not been demonstrated beyond doubt, the following steps may be involved: passage of O_3 through the upper respiratory tract, interaction with airway surface liquids, which produces reactive compounds, and stimulation of rapidly adapting receptors, which results in the inability or unwillingness of the subject to inspire maximally. The point or points in the pathway that account for the large differences in responsiveness may have a bearing upon the implication of these differences. If the intersubject differences occur solely in the central nervous system at the level of perception of discomfort, the more responsive subjects may have no more changes in the airways than do the less responsive. On the other hand, if this variability is due to differences in the efficiency of O_3 removal in the nasopharynx, the more responsive subjects will clearly suffer greater insults to the airways. Because chronic effects of recurrent ambient O_3 exposure in humans have not been observed, it is not clear whether intersubject differences in acute O_3 responsiveness have any bearing upon possible chronic effects. If, however, a surrogate for acute O_3 responsiveness could be identified, it would be very useful to stratify subjects on the basis of O_3 responsiveness in subsequent epidemiologic studies of the effects of recurrent O_3 exposure.

The reproducibility of responses measured by other variables can be evaluated by examining the R for each variable (table 2). Changes in FEF_{25-75} and the symptom cough were the next most reproducible variables. Much like FVC and FEV_1, these variables were reproducible at all levels of O_3 greater than or equal to 0.18 ppm, and were somewhat more variable with increasing time between exposures. The same conclusions can be drawn for these variables as were drawn for FVC and FEV_1. Although the extent to which intersubject variability in response can be attributed to differences in intrinsic responsiveness to O_3 is less, it is still considerable. A partial explanation for the poorer reproducibility of cough is due to the discrete nature of the data and the imprecision inherent in quantifying subjective responses. The reasons for the poorer reproducibility of FEF_{25-75} are unclear. In the absence of other well-characterized surrogates for O_3 responsiveness, a history of coughing during high ambient O_3 episodes may be a useful measure upon which to stratify epidemiologic data.

Responses as measured by SRaw and shortness of breath were less reproducible still, and pain upon deep inspiration, f, and V_T were not reproducible. The baseline values of f and V_T were less reproducible than for other variables (data not presented), probably because of their dependence on even smaller changes in work load. The poor reproducibility for shortness of breath and pain upon deep inspiration is at least partially due to the difficulty in quantifying these symptoms. Because exercise alone at this level induces these symptoms in some subjects (3), these measures include the variability caused by both exercise and by O_3 exposure. A partial explanation for the poor reproducibility of changes in SRaw is that measures of SRaw are less repro-

ducible over any period of time than are spirometric measurements (table 1). We have no explanations other than chance for the increasing reproducibility of SRaw measurements with increasing time.

For all variables, the R at 0.12 ppm was generally lower than at the other O_3 levels. This was primarily due to the relatively small range of intersubject differences for the group of 8 subjects exposed to 0.12 ppm O_3. A larger sample would probably result in a somewhat larger range of response and may result in an increased R. A similar phenomenon was observed for the 0.30 ppm group. The range of response for this group was limited (figure 1), relative to the 0.18, 0.24, and 0.40 ppm groups. This is most likely due to chance, however, whereas the small range at 0.12 ppm was primarily due to the lack of specific O_3 response or a uniformly small response in the majority of subjects.

In summary, we have demonstrated that individual responses to O_3 as measured by FVC and FEV_1 are highly reproducible for periods as long as 10 months, and responses measured by cough and FEF_{25-75} are somewhat less so. These responses are quite reproducible at levels of O_3 greater than or equal to 0.18 ppm O_3 and less so at 0.12 ppm. A slight decrease in responsiveness with time was suggested. These results indicate that the reported large intersubject variability in magnitude of response is due to large differences in the intrinsic responsiveness of individual subjects to O_3 exposure. One implication of this is that some subjects exposed to O_3 under ambient conditions will reproducibly have larger acute responses than will others. The implications of this intersubject variability for recurrent exposures are unknown.

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